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# Recent progress in regenerative medicine for brain disorders

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## Introduction

Regenerative medicine for central nervous system (CNS) disorders using cell-based therapies represents an exciting area that requires significant preclinical research. Current evidence suggests that stem cell-based therapies could be molded into treatment strategies for a wide-variety of neurological disorders by enhancing the endogenous neuroplasticity of the CNS. Traumatic brain injury (TBI), stroke, epilepsy, Parkinson's disease (PD) along with several other chronic neurodegenerative disorders are debilitating diseases that have few treatment options. Cell therapy may offer beneficial effects for these disease indications. Many tissues have been identified as rich sources of different types of stem cells. In this special issue, we focus on mesenchymal stem cells (MSCs) and amniotic membrane (AM)-derived stem cells as candidates for cell transplantation therapy. Overall, the techniques, timelines, route of administration and the underlying mechanisms, as well as the safety and efficacy of cell therapy still require further research to translate this treatment into a routine clinical application.

The following 10 articles span various important recent areas of research in regenerative medicine for CNS disorders from scientists who gathered at the 2017 Annual Meeting of the American Society for Neural Therapy and Repair held in Clearwater, Florida. This editorial outlines not only the significant results from each individual study but also places a focus on the future directions needed to advance cell

therapies to the clinic as a safe and effective treatment for neurological disorders.

## Examining Neurogenesis in Preclinical Model that Replicates "Immobilized State" of Neurological Disorders

### Chapter 1 - Limiting exercise inhibits neuronal recovery from neurological disorders

Exercise has been noted for its therapeutic potential to treat neurological disorders. However, many of these neurological disorders immobilize patients causing muscular atrophy, decreased activity and depression. Here, the authors investigated the neurological effects of a lack of exercise. This study suggests that immobilization suppresses circulating trophic and growth factors which limit neurogenesis. Future preclinical research is needed to determine therapeutic procedures to target decreased neurogenetic factors to combat the negative outcomes of decreased exercise. In addition, improved biomarkers to better detect growth factors, stress-related proteins and stem cell alterations for future studies.

## Therapeutic Potential of Cell Therapy, Pharmaceuticals and Relevant Treatments to Enhance Neurogenesis for Various Neurological Disorders

**Chapter 2 - Exogenous stem cells pioneer a biobridge to the advantage of host brain cells following stroke: New insights for clinical applications**  
Stroke is a major cause of death for Americans and inflicts a significant economic cost to

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the world, but there remain very few viable treatment options. Stem cells are an untapped potential treatment area that could function to facilitate neurological repair for many disorders. In this paper, the authors proposed a biobridge model where exogenous transplanted stem cells interact with endogenous stem cells further enhancing the therapeutic outcomes of stem cells. The biobridge would form a biological link between the neurogenic niche and stroke- or TBI-affected tissue to promote neurogenesis in the damaged areas. Since multi-faceted cell death pathways accompany many neurological disorders, a multipronged therapeutic approach is likely an effective treatment method. Through multiple regenerative mechanisms such as cell replacement, bystander effects, and the biobridge formation, stem cell therapy could prove effective for stroke and other CNS disorders.

### **Chapter 3 - Neuroinflammation in traumatic brain injury: A chronic response to an acute injury**

Recognizing the prevailing theme of TBI as an urgent unmet clinical need, the authors reviewed the etiology, symptoms and therapeutic treatments for TBI. The primary phase of TBI causes significant necrotic death but due to the acute timeline, treatment options during this phase is very limited. However, significant damage occurs during secondary cell death due to neuroinflammation. Secondary cell death is instigated by excitotoxicity, blood-brain barrier breakdown, oxidative stress, and inflammation. Inflammation is a major contributor to secondary cell death and a likely therapeutic target through anti-inflammatory mechanisms. Targeting specific factors, proteins, genes and utilizing stem cell therapy, such as MSC treatments, to target anti-inflammatory responses could produce therapeutic outcomes. A greater understanding of TBI etiology and neuroinflammation pathology is necessary to improve clinical anti-inflammatory treatments.

### **Chapter 4 - Granulocyte-colony-stimulating factor and umbilical cord blood cell transplantation: Synergistic therapies for the treatment of traumatic brain injury**

Along the same topic of TBI, the authors advance the concept of combinational TBI treatment. As previously mentioned, current TBI preclinical studies target the secondary phase of brain injury using stem cell therapies to enhance neurogenesis and repair damaged tissues. A potent therapeutic approach to provide the best recovery is through combination therapy. In this study, human umbilical cord blood cell (hUCB) therapy and granulocyte-colony-stimulating factor (G-CSF) demonstrated therapeutic outcomes alone, but in combination, they significantly enhanced neurogenesis, anti-inflammatory effects and increased cell survival

in TBI rats. Further research is needed to examine the mechanisms underlying the therapeutic outcomes of hUCB and G-CSF combination therapy and to determine the safety and effectiveness as a clinical treatment.

### **Chapter 5 - Drug treatments that optimize endogenous neurogenesis as a therapeutic option for stroke**

Stroke leads to significant neural death. However, stroke also induces spontaneous neurorepair, although not sufficient enough to halt the disease progression. Neurogenesis is seen in the subventricular zone (SVZ) several days poststroke, but most of these cells die. The authors aimed to enhance this endogenous reparative process through pharmaceutical treatment. This review study analyzes several endogenous neurogenesis-enhancing drugs, such as Pifithrin- $\alpha$ , cocaine and various trophic factors, such as bone morphogenetic protein 7 and brain-derived neurotrophic factor (BDNF) along with dietary supplementation. These drugs represent promising potential therapeutic routes due to their ability to enhance neurogenesis, practically in the SVZ. Despite this encouraging evidence, there remains a need for the optimization of the drug delivery route, dosage, and timing, along with further preclinical research on the effects and mechanisms of these drugs. Finally, studies investigating the possible combination therapy potential of these drugs warrants investigation.

### **Chapter 6 - Translating regenerative medicine techniques for the treatment of epilepsy**

Epilepsy is a chronic neurological disorder that causes seizures in diagnosed patients and has conventionally been treated with antiepileptic drugs. The authors discussed the recent and novel preclinical treatments for correcting epilepsy. In this review, they focused on three primary treatment strategies. First, through cell therapy utilizing mesenchymal and neural stem cells' neuroprotective effects to create a therapeutic outcome on specific GABAergic neurons. In addition, neuroprotective agents, such as BDNF and erythropoietin which demonstrate promising neuroprotective potential. Finally, utilizing electrical stimulation, specifically vagal nerve stimulation along with more controversial deep brain stimulation, epidural stimulation, and transcranial magnetic stimulation to correct epilepsy. Overall, these therapeutic treatments require further preclinical research to better understand the treatment procedures, timing, disease pathology, and mechanisms underlying epilepsy.

### **Chapter 7 - Endogenous repair mechanisms enhanced in Parkinson's disease following stem cell therapy**

PD is a chronic brain disorder that represents a significant neurological disorder in many aging

adults and requires further stem cell research. The authors provided an overview of recent progress in cell therapy for PD. Deviating from the traditional cell replacement mechanism, the authors highlighted the alternative regenerative pathway of bystander effects. They recognized significant factors in the SVZ, such as proteasomes, neurotrophic factors and anti-inflammatory cytokines and their role in generating therapeutic outcomes. Cell therapy is shown as a promising therapeutic option for PD, but it still requires an in-depth understanding of its underlying pathology and treatment mechanisms.

### **The Amniotic Membrane and Fluid as an Ethical Stem Cell Source for Modeling Genetic Diseases and Producing Therapeutic Outcomes**

#### **Chapter 8 - Amniotic fluid stem cell models: A tool for filling the gaps in knowledge for human genetic diseases**

Generating induced pluripotent stem cells can be costly, time-consuming, sometimes ineffective and can raise ethical concerns. However, amniotic fluid stem (AFS) cells represent a new alternative source for future stem cell generation and are ideal because AFS cells can be easily and noninvasively collected from women undergoing amniocentesis while avoiding ethical concerns. The authors analyzed the safety, efficacy, and relevance of AFS cells in reprogramming for human diseases and drug testing. From this review, they noted that AFS cells maintain pluripotency and can undergo a large-scale amplification demonstrating their potential in creating models to test pharmaceutical drugs. AFS cell therapy still requires significant research to develop models, techniques and determine the effectiveness. Of note, the novel genome editing technique, CRISPR, represents an excellent way to generate *in vitro* models to study specific disease pathologies by utilizing AFS cells.

#### **Chapter 9 - Amniotic fluid as a source of engraftable stem cells**

Research into stem cell sources for cell transplantation is very important and the authors recognized the potential of the AM as an effective source for stem and progenitor cells. This review focuses on the abilities of human amniotic epithelial and mesenchymal stromal cells derived from the AM, in addition to the therapeutic effects of the AM on treating tissue inflammation. Human amniotic epithelial cells and human amniotic mesenchymal stromal cells maintain pluripotency and can differentiate into multiple cell types and undergo passages. From the results, the AM and the AM-derived cells showed strong anti-inflammatory and anti-fibrotic

effects when treating various disease models. In future directions, there remains a need to further develop the treatment techniques and procedures for AM-derived stem and progenitor cells, along with developing the mechanisms, safety, and effectiveness.

### **Combating Radiotherapy-induced Neurological Deficits Through Adjunctive Treatments**

#### **Chapter 10 - Colony stimulating factor 1 receptor as a treatment for cognitive deficits postfractionated whole-brain irradiation**

Whole brain irradiation (WBI) is a common treatment for CNS tumors and brain metastases and increases survival. However, the symptoms of this treatment are often detrimental to the patient's cognitive abilities and the mechanisms underlying these deficits are not well researched. The authors sought to target colony stimulating factor-1 receptor (CSF-1R) as a treatment option to combat the side effects of WBI. They demonstrated that pairing a CSF-1R inhibitor along with the fractionated WBI treatment decreased the amount of resident and peripheral mononuclear phagocytes, the dendritic spine loss and reduced the functional and memory deficits. This treatment shows promising evidence for counter-treatments to lessen the negative side effects of WBI. However, further research is needed to optimize treatment strategies, the treatment timeline and to further understand the mechanisms behind WBI and the long-term side effects of targeting CSF-1R as a treatment strategy.

### **Conclusion**

Cell-based therapies for CNS disorders show strong potential in nurturing regenerative medicine. Harnessing the pluripotent potential of stem cells could enhance the therapeutic outcomes of regenerative medicine. Most of this work remains in the preclinical stages, with limited clinical trials being pursued over the last decade. The translational preclinical research focused on optimization of transplant regimen and its mechanism of action, either as stand alone or in combination and tailored for a specific neurological disorder will likely guide the successful application of this novel treatment in the clinical setting.

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#### **Conflicts of Interest**

Nil.